Southwestern MEDICINE

Official Journal of The Southwestern Medical Association, The Western Association of Railway Surgeons, The Texas Orthopaedic Association, The Southwest Obstetrical and Gynecological Society, The Southwestern Dermatological Society, Texas District One Medical Association, The Southwestern New Mexico Medical Society, and El Paso County Medical Society

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December, 1960

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1. Stephens, V. C., *et al.:* J. Am. Pharm. A. (Scient. Ed.), *48:*620, 1959.
2. Salitsky, S., *et al.:* Antibiotics Annual, p. 893, 1959-1960.
3. Reichelderfer, T. E., *et al.:* Antibiotics Annual, p. 899, 1959-1960.
4. Kuder, H. V.: Clin. Pharmacol. & Therap., in press.

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Coming Meetings

American Rheumatism Association, Seventh Interim Scientific Session, Sheraton-Dallas Hotel, Dallas, Dec. 9-10, 1960.

American Cancer Society, Arizona Division, Ninth Annual Cancer Seminar, Tidelands Motor Inn, Tucson, Jan. 12-14, 1961.

International Medical Assembly of Southwest Texas, 25th Annual Meeting, Granada Hotel, San Antonio, Jan. 23-25, 1961.

Arizona Heart Association, Fourth Annual Cardiac Symposium, Biltmore Hotel, Phoenix, Jan. 27-28, 1961.

Texas Orthopaedic Association, Galveston, Texas, April 24, 1961.

Postgraduate Course To Be Held in El Paso, Jan. 22

A one-day course on Obstetrics and Gynecology will be presented January 22, 1961, by the El Paso Branch of the University of Texas Postgraduate School of Medicine at the El Paso County Medical Society's Turner Home at 1301 Montana Ave. Dr. J. Leighton Green is director of the El Paso branch.

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SOUTHWESTERN MEDICINE

VOL. XLI, NO. 12 DECEMBER, 1960

Dr. Burr of Tucson Elected President of Southwestern Medical Association

Dr. Sherwood Burr of Tucson was elected president of the Southwestern Medical Association at its 42nd annual meeting in El Paso October 20-22, 1960.

Other new officers are Dr. Harold J. Beck, Albuquerque, president-elect; Dr. David Russek, Chihuahua City, Mexico, vice-president; and Dr. Merle D. Thomas, El Paso, who was re-elected secretary-treasurer.

New members of the executive committee are Dr. John Dettweiler, Albuquerque; Dr. Russell L. Deter, El Paso, retiring president; Dr. Louis G. Jekel, Phoenix; Dr. Leland Evans, Las Cruces, N. M.; Dr. Darwin Neubauer, Tucson; Dr. Carlos Tapia, Hermosillo, Mexico; and Dr. Louis W. Breck, El Paso, managing Editor of **Southwestern Medicine.**

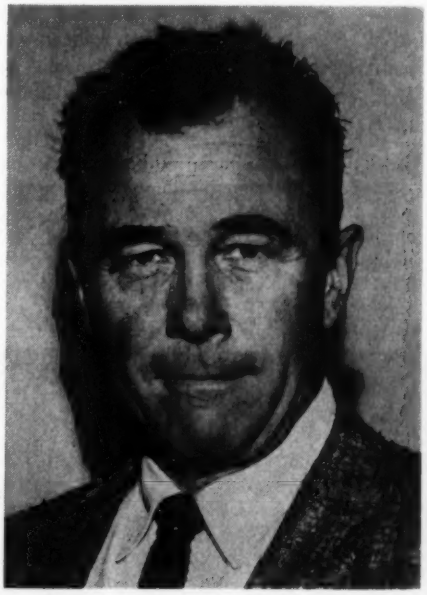
Las Vegas, Nevada, was selected as site for the 1961 meeting, which will be held October 19-21, 1961. Headquarters for the meeting will be in the Tropicana Hotel.

Speakers

Speakers were: Dr. Ernest Craige, associate professor of medicine at the University of North Carolina School of Medicine; Dr. Donald Stubbs, clinical professor of Anesthesiology at George Washington University Medical School and chairman of the board of Blue Shield.

Dr. Philip J. Hodes, professor and chairman of the Department of Radiology at Jefferson Medical Center in Philadelphia; Dr. Henry N. Harkins, professor of surgery at the University of Washington in Seattle.

Dr. Harold W. Brown, clinical professor of ophthalmology at New York University, Bellevue Medical Center; and Dr. Ernest E. Muirhead, professor and chairman of the department of clinical pathology at Wayne University in Detroit.



Dr. Burr

Dr. Charles E. Irvin, Ormond Beach, Fla., well known as the "Merchant of Message," spoke on "The Inside Story of an Outside Chance" at the association's annual banquet.

The new president, Dr. Burr, was born in Eugene, Ore., and received his B.A. at the University of Oregon and his M.D. at the University of

Oregon School of Medicine. He holds an M.S. in ophthalmology from the State University of Iowa. He interned at the University of Oregon Hospitals and Clinics and then took a four-year residency at the State University of Iowa Medical School.

He began the practice of medicine in 1948 in Bakersfield, Calif., and in 1949 moved to Tucson, where he at first was associated in practice with Dr. C. S. O'Brien, who was his professor in ophthalmology at the State University of Iowa and who is now retired. His offices are at 45 N. Tucson Blvd., where he is associated with Dr. James Calkins and Dr. A. K. Hansen.

Dr. Burr is certified by the American Board of Ophthalmology and is a Fellow in the American Academy of Ophthalmology and Otolaryngology. He is a member of the Association for Research and Ophthalmology and the Pan American Ophthalmological Association. He is a consultant in ophthalmology at the Davis Monthan Air Base, the veterans hospital, and the Arizona Children's Colony in Coolidge, Ariz. During World War II Dr. Burr served as a flight surgeon in the Air Force with 40 months in the Pacific Theatre, emerging with the rank of lieutenant colonel.

He is a member of Nu Sigma Nu, Phi Delta Theta, Rotary Club and St. Michael's Episcopal Church. He and his wife reside at 3135 Via Palos Verdes with their three children, Minda 12, Sherwood, Jr., 10, and Bradley, 8.

Presidential Address

In his presidential address at opening of the association's meeting, Dr. Deter charged that the United States has already gone far down the road to socialism and he urged physicians to join the fight for the preservation of free enterprise.

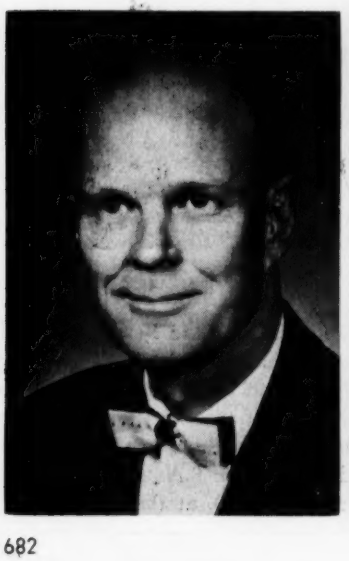
"We have got to keep the boat from going over the rapids," he said. "The time has come when we as physicians are in position to tell the story of the American system. We should go out and sell free enterprise to our patients."

Dr. Deter took a slap at Government farm support prices and said, "We are no more responsible for failure on the farm than anywhere else. If farmers cannot succeed on the farm in a given period of time they should give it up. Suppose we had started to support the harness industry when the horse began to go out—we'd have one hell of a pile of harness on hand now."

He said that "dictators always look good—until the last ten minutes."

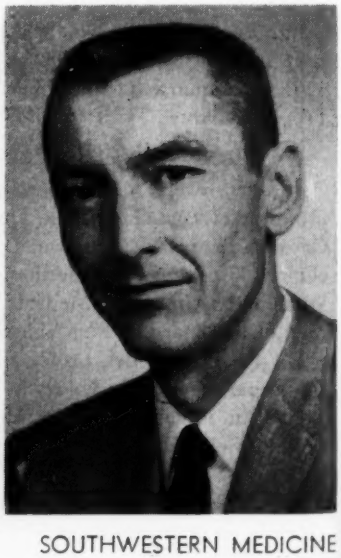
"We have only one thing to sell—skill," he said. "Skill has to be delivered to the consumer. Not answering the telephone or not making house calls is not delivering our skills."

Dr. Beck



Dr. Russek

Dr. Thomas



Ten Point Plan to Improve Health of 675,000 Texans Drafted by Dr. Deter

The Texas Medical Association has set forth a ten-point plan of action designed to improve health care for the 675,000 Texans who are 65 years of age or older. The plan was drafted by Dr. Russell L. Deter, El Paso, Vice President, who is coordinating many Association Committee activities in the field of aging. Dr. Deter also serves as Co-Chairman of the Sub-Committee on Health to the Texas Governor's Conference on Aging, and has been appointed as a delegate from Texas to the White House Conference on Aging.

Text of the plan is as follows:

1. Responsibility for Care: In keeping with American traditions, the individual has the primary responsibility for his own medical care. When the individual is unable to provide this care for himself, the responsibility rightfully should pass to his family, then to the community, the county, and the state. Only when all of these fail should the federal government assume a role, and then only in cooperation with other governmental bodies cited previously. Specifically, the federal government should not assume the full responsibility solely upon the basis of default by local and state resources.

2. Role of Physician: Physicians, by tradition, have a responsibility to provide professional services to his patients, regardless of ability to pay. Physicians will continue, as they have in the past, to provide medical services for the aged, including the indigent and the near needy, at fees they can afford, or without charge, as their resources might indicate.

3. Voluntary Health Insurance: Voluntary health insurance is an effective mechanism for financing health care costs, and coverage should be extended to as many of the aged as is practicable and possible. Special health insurance and prepayment policies which are tailored to meet the needs of the aged should continue to be developed and promoted. In addition, in order to achieve the long-term objective of extensive coverage, all individuals in younger years who are gainfully employed should be encouraged to purchase voluntary health insurance which will carry over beyond age 65, either on a paid-up basis or by permitting individuals to continue coverage following their retirement.

4. Assistance Programs for Indigent and Needy: Programs of health care are available to the indigent through Old Age Assistance. The 86th Congress enacted legislation providing for federal grants-in-aid to the states to help pay medical and hospital bills of needy persons 65 and older. The House of Delegates of the Texas Medical Association is on record favoring the State vendor's medical care program, and the Association will lend its full support in implementing a plan which provides high quality medical care, and embraces such basic principles as free choice of physician and preservation of the traditional doctor-patient relationship. The vendor's medical care program should be limited only to those who need help, and should not include those who can provide for themselves.

5. Personnel and Facilities: To keep apace of the demands of an expanding population, and the increasing number of older people, the Texas Medical Association recognizes the need for additional personnel in the medical sciences and for more facilities. The House of Delegates has advocated the erection of a fourth medical school in the State. The first step toward this objective has been realized with the authorization of a new medical school by the State Legislature. Similar attention must be given to educating professional and allied health personnel who assist the physician in the care of the patient. Nursing resources particularly must be enhanced. More students should be recruited, and encouragement, should be given to the Association's Woman's Auxiliary and other groups which sponsor Future Nurses Clubs. Many graduate nurses who have become inactive should be provided opportunities to return to their profession. Nursing educational and training programs should be expanded. The Association should continue to work for better nursing home facilities for the long-term care of aged persons. Particular attention also must be given to the establishment of additional facilities for the care of the chronically ill, for rehabilitation, and for neuropsychiatric care.

6. Home Nursing Care: Care of the aged at home is psychologically, medically, and financially desirable. The Association encourages the development of programs to promote home nursing care. These include homemaker's services, which provide opportunities for those caring for aged mothers and fathers to continue gainful employment; central counseling and day care agencies; visiting nurse services, and rehabilitation resources.

7. Organizational Endeavors: For many years, the Texas Medical Association has had an active Committee on Aging. This Committee has intensified its activities, and educational endeavors in recent years in order to implement a multi-phased program. Many other Association committees, such as Voluntary Health Insurance and Patient Care, continue to contribute in their fields of responsibility. The present high interest of the Association is reflected in the action of the 1960 House of Delegates which charged the Vice-President to

coordinate all activities in regard to health care for the aged. In addition, the Texas Medical Association has joined hands with the Texas Dental Association, the Texas Hospital Association, and the Texas Nursing Home Association to form the Texas Joint Health Council for the Aging. The Texas Medical Association has urged each of its component county medical societies to activate a Committee on Aging, and to assume leadership in worth-while programs, such as the promotion of more and better nursing home facilities and in sponsoring well-adult conferences on aging.

8. Educational Activities: The Texas Medical Association encourages broad educational programs at all levels to educate and prepare men and women to face the problems of aging more resourcefully. For all of the health professions, special instruction should be included in undergraduate curricula and in post graduate courses. The Association also recognizes the need for increased health education activities, such as a statewide informational program for the elderly on the importance of periodic health examinations and the role of preventive medicine in maintaining good health. Educational programs in accident prevention, designed specifically for the aged, also deserve attention. Many older persons are unaware of the need for continuing healthful nutrition and other practices which contribute to health. Above all, the "Will to Live" is essential to continuing health.

9. Attitude Toward Aged: A basic change in attitude toward the aged is imperative. The individual who attains age 65 does not suddenly become non-productive and senescent. On the contrary, most persons 65 and older are reasonably well, and many are willing and able to work. The Texas Medical Association lends its full support to assisting the elderly to attain increased productivity by eliminating compulsory retirement provisions and by permitting voluntary change of work.

10. Purchasing Power of the Dollar: Economic problems of the aged have been intensified during the past 20 years by the constant and continuing erosion of the purchasing power of the dollar and by increasing taxes which claim a larger share of fixed incomes. Psysicians and professional men and women, business and industry, labor, and government can make a significant contribution to the economic welfare of the aged by refraining from embracing those activities which are inflationary in character, and by helping to maintain the purchasing power of fixed pension and annuity benefits.

To implement the 10-point program, it is recommended that:

1. The Texas Medical Association give firm backing to the recommendations of the Health Subcommittee of the Governor's Conference on Aging.

2. County medical societies initiate a state-wide program on the very special problems of aging, other than the disease processes.

3. County medical societies institute education of elderly individuals on the importance of:

- **a.** Periodic health examinations and preventive medicine in the maintenance of good health.
- **b.** Strong accident prevention education to the elderly.
- **c.** Proper nutrition in maintenance of good health.

4. County societies undertake an active program on improving quality and quantity of nursing homes and nursing home personnel, as well as better medical supervision of these nursing homes.

5. County societies should take leadership in well-adult conferences on aging.

6. County societies institute programs at all levels —professional and lay—to train young men and women to face the problems of aging more resourcefully.

7. County medical societies and the Texas Medical Association devote considerably more effort to nurse recruitment, increasing numbers of nursing schools and making a determined effort to solve the problems of the registered nurse shortage in Texas. (Your attention is particularly called to recommendation No. 4 Health Subcommittee, Governor's Conference on the Aging.)

8. Texas Medical Association encourage establishment of additional chronic and convalescent or terminal care units in connection with new and existing hospitals.

9. The Texas Medical Association and each county society in urban areas, and in many instances rural areas, make a concerted effort to establish a local committee on aging, as outlined in Recommendation No. IX, Subcommittee on Health, Governor's Conference on the Aging.

10. All county societies be urged to use what facilities are available locally, wherever possible, and not establish new organizations which would be a duplication of effort when a similar organization is already doing the job and merely is in need of more help. Don't let us be guilty of promoting "edifice complex" in our local government.

So that the Texas Medical Association not become the benevolent parent who is going to do all of these things for the individual physician and the individual county medical society, each county medical society is charged with the responsibility of forwarding to the Executive Secretary of the Texas Medical Association a semi-annual progress report on the above recommendations. The Executive Secretary then will present an annual progress report to the House of Delegates.

Santa Fe Seminar

St. Vincent Hospital, Santa Fe
May 24, 1960

Chairman: Harry D. Ellis, M.D.
Case Presentation: Fred Soldow, M.D.
Seminar Summary: Matthew Tandysh, M.D.

Hemolytic Disease of Newborn

Dr. Harry Ellis:

The cases selected for presentation this evening illustrate many of the variable problems encountered in hemolytic disease of the newborn, and I think they also point out that locally we are making progress in our management of these problems. Dr. Fred Soldow will present the cases in summary form. Dr. Soldow.

Presentation of Case Summaries: Dr. Fred Soldow.

Case No. 1 T. A. W.

On September 27, 1955, a 7 lb. 5 oz. baby girl was delivered normally at St. Vincent Hospital. The baby was very pale and its cry was weak.

The skin was yellow at birth and its subcutaneous tissues felt edematous. The spleen was palpable, reaching to the iliac crest. The liver was down two fingers.

Laboratory examinations revealed a hemoglobin of 5.4 grams and a WBC of 77,600 per cmm. which included many nucleated red blood cells.

Positive Coombs Test

The direct Coombs test was positive and the serum bilirubin level was 110 mg/100 ml.

The past history revealed that a sibling had been delivered in similar condition and had been given an exchange transfusion. Two children previous to this were normal. Shortly before this delivery the mother had an anti D antibody titer of 1-80.

Two hours after delivery an exchange transfusion was carried out. The subsequent clinical course was uneventful and the baby was discharged in good condition.

Case No. 2 B. E. W.

On July 7, 1954, a one month premature, 4 lb. 10 oz. male baby was delivered normally at St. Vincent Hospital. Examination at birth revealed a suggestion of jaundice and at two hours of age the baby was definitely jaundiced.

The past history revealed one previous child, living and well. There were no previous miscarriages and no previous transfusions. The mother was Rh^o positive and her serum contained no anti Rh^o antibodies.

Laboratory data: WBC 19,000/cmm. with six nucleated RBC/100 WBC. Hgb. 22.3 grams.

Coombs test: Negative. Baby's blood type: A Rh^o positive. Complete blood type A $\frac{CDe}{C\text{-}e}$. Mother's type: O $\frac{CDE}{C\text{-}e}$. Father's type: A $\frac{CDe}{C\text{-}e}$

Anti-A Antibodies

Immune anti A antibodies were found later in high titer in the mother's serum (7/15/54).

Following birth, the baby's hemoglobin fell to 19.0 grams over a period of three days and then to 16.5 grams in the subsequent three days. On 7/10/54, mild opisthotonos was noted and jaundice was marked. The liver was felt two fingers below the right costal margin and the spleen was not palpable. On 7/11/54, opisthotonos was increased and the deep reflexes were increased.

By 7/15/54, the jaundice was clearing and neurologic symptoms were subsiding. On 7/19/54, the baby was discharged in fairly good condition. Subsequently, the baby developed cerebral palsy and a hearing defect.

Case No. 3 J. P. R.

On May 10, 1960, a 6 lb. 2 oz. male baby, delivered normally, now age 40 hours, was admitted as a transfer from another hospital. The referring physician stated that the baby became jaundiced at the end of 24 hours. At 38 hours of age, the serum bilirubin was 11.1 mgs per cent and

this was almost all indirect reacting bilirubin. The hemoglobin was 18 grams. The baby had developed by this time moderate jaundice.

Bilirubin 20 Mgms/100 ML

Shortly after admission to St. Vincent Hospital, the hemoglobin was found to be 20 grams and the serum bilirubin (mostly non-conjugated) was 19.5 mgms/100 ml.

The direct Coombs test was negative. The baby's blood type was O Rh° positive. The mother's blood type was A Rh° negative.

Laboratory studies also revealed an indirect Coombs test using maternal serum and baby's cells to be negative.

The maternal history revealed a miscarriage one year prior to this child, no previous transfusions and no other children. The physician who delivered this baby also delivered the mother and four siblings of the mother and found in his records that the mother and her four siblings had all been more jaundiced than usual after birth. This information was also given by the maternal grandmother.

Normal Except Icterus

Examination of the baby on admission revealed normal findings except for moderate icterus. The liver was down one finger and the spleen was not felt.

Observation of the baby for 24 hours revealed no increase in serum bilirubin and no decrease in hemoglobin level.

The baby was discharged in good condition 5/11/60.

Dr. Ellis:

We are fortunate this evening in having Dr. Matthew Tandysh with us. As most of you know, Dr. Tandysh is in practice in Albuquerque and is one of our state's outstanding pediatricians. I would also like to welcome Dr. Tandysh's residents who have come with him here tonight for the seminar. Dr. Tandysh.

Discussion: Dr. Matthew Tandysh:

I received a copy of the presentation prior to coming here so I cheated a little bit and studied it before hand.

The first case is very interesting in that it represents at least a mild type of hydrops which is a most severe type of newborn hemolytic disease.

I was surprised in reading the case summary to see that after only one exchange transfusion, the baby did so well. With a hemoglobin of 5.4 grams, I'm sure that there was some cardiac failure. There is nothing mentioned about pulmonary edema and I guess the baby didn't get into any trouble. Here is a baby who was Rh° positive born to a mother with a high titer, who received an exchange transfusion at two hours of age, which is optimum timing. Actually, I've seen these start within minutes after the baby's delivery.

Anticipate Trouble

This is indicated in situations where you know that the mother has lost a child because of hydrops and you know that the father is Rh° positive and homozygous. Then you certainly can anticipate trouble. In such circumstances an exchange transfusion ought to be anticipated prior to the delivery of the child.

The second case is interesting in that you don't have any mention of serum bilirubin, only that the baby appeared yellow. This case represents hemolysis due to an antibody different from an Rh antibody, namely an immune A antibody.

We are now aware that more than 50 per cent of all hemolytic disease of the newborn results from this type of sensitization, rather than from Rh sensitization. Here is a mother who is type O and the baby type A. The mother had a very high anti A titer and I'm sure that this was the major element producing the baby's jaundice.

Immaturity

Another contributing factor is immaturity. We know that bilirubin is conjugated in the liver with glucuronic acid which makes it easier to excrete. With immaturity there is an inability to conjugate bilirubin from the indirect to the direct form, often leading to an accumulation of this apparently toxic material.

The last sentence that the baby developed cerebral palsy and a hearing defect subsequently is interesting because we know that kernicterus in the neonatal period is responsible, or can be responsible for this. We also know that prematurity has a high incidence of mental deficiency, cerebral palsy, and other nervous system defects.

Four Consequences

As an aside, Dr. Richard Day from Pittsburgh, while at the recent State meeting in Albuquerque, mentioned that there are four consequences of

hemolytic disease of the newborn. One was death, either immediate or subsequent; another was mental retardation; the third was cerebral palsy and various neurological deficits; and the fourth, he said with a wry smile, was a law suit.

Then he discussed the case of a child who was mentally defective, having had a high neonatal bilirubin and two exchange transfusions. The problem was the exact etiology of the retarded mentality. We know that children who are born jaundiced can suffer unrelated retardation.

The third case is probably accentuated physiological jaundice. The baby did not receive an exchange transfusion and actually an exchange transfusion was not indicated. I think most of the authorities feel that only if the indirect or the non-conjugated portion of the bilirubin reaches or approaches 20 mgs., is an exchange indicated. This child's jaundice appeared late. It was transferred after it was 40 hours of age. We know that the hemolytic types of jaundice appear usually within the first 24 hours whereas the physiologic type is more insidious. The latter type often leads to little loss or depletion of hemoglobin.

Hemoglobin 20 Grams

This baby's hemoglobin was 20 grams shortly after admission to St. Vincent Hospital and decreased only a little. An interesting side light concerning hemolytic disease is that when the Rh factor was discovered some investigators wondered why a mother who had had two or three previously hydropic babies would suddenly deliver a baby who became jaundiced the second or third day, never required an exchange transfusion, and then did very well.

It was subsequently learned that there may be competition between A and Rh antigens. When a mother who is Rh negative, type O, carries an Rh positive baby, type A, some of the baby's blood cells may go through the placenta into the mother's system and there stimulate antibody production. In such a case antigen A (or B) may take preference over Rh.

Dr. Ellis:

Thank you, Dr. Tandysh. The next discussion is listed as kernicterus, but it will include discussion of some other basic problems. Dr. Carol Smith.

Kernicterus: Dr. Carol Smith.

In simple terms kernicterus may be defined as greenish yellow staining of the nuclei of the brain, particularly the basal ganglia. It seems to be a little more selective in that area. This usually leads to such permanent brain damage as greater or lesser degrees of spasticity, choreo-athetosis, mental retardation, deafness, blindness, etc.

You may have death in a few days to weeks if the process is sufficiently severe. It is also of interest that until recently, approximately 10 per cent of all children admitted to institutions for the mentally retarded had as their etiology, kernicterus.

Etiology of Kernicterus

What is the etiology of kernicterus? The normal red cells break down in all of us and that includes the newborn. Bilirubin and other compounds are derived. Bilirubin is apparently the offender here. Normally bilirubin is converted into a bilirubin glucuronide which is so-called direct bilirubin. In field mice, it is believed that this conversion may occur via placental factors in the fetus but no one is really sure about that. It is then excreted as direct bilirubin or bilirubin glucuronide. In the newborn and especially in the premature newborn, glucuronides are very poorly formed so that there is normally a higher concentration of indirect or unconjugated bilirubin present in the blood.

As a side point, it is of interest that the administration of intravenous glucuronic acid in neonates with severe jaundice has not been very rewarding. It is an avenue of research that is still being pursued.

It is believed that indirect bilirubin is probably converted to a mesobilirubin within the brain and deposited in the nuclei as such and here it interferes with the normal metabolism of brain cells, particularly with phosphorylation, and so leads to necrobiosis.

The blood brain barrier is also known to be less mature in the premature infant than in the full term infant. Therefore, although many believe that this process is reversible in its early phases, it is often more severe and of more clinical importance in the premature infant.

Many Causes of Bilirubinemia

There are many causes of hyperbilirubinemia. The hemolytic diseases of the newborn are probably the most important ones confronting us but they are not the most numerous.

The commonest forms of hemolytic disease of

the newborn are those concerned with the Rh and the ABO antigens.

There was an interesting report in one of the pediatric journals recently on familial sperocytosis, that is congenital hemolytic anemia, in which the baby had a crisis on the second day of life and its serum bilirubin reached 35 mgms/100 ml. This baby received an exchange transfusion and made an uneventful recovery.

Other factors which are important in the production of hyperbilirubinemia are the so-called non-hemolytic diseases of the newborn. The most important one of these is physiologic jaundice. I think case No. 3 falls into this category.

Physiologic jaundice appears in all infants. If we did routine bilirubins on every infant in the nursery, we would find a rise above the so-called normal adult level. And in infants with less mature liver function, the bilirubin may rise as high as 30 mgms/100 ml. or more.

Exchange Indicated

If the bilirubin is rising rapidly, regardless of whether or not there is hemolytic disease, an exchange transfusion is indicated. There are a number of cases reported who developed kernicterus on a basis of apparent physiologic jaundice. Many people feel that it is safe to watch for irritability and feel that if the bilirubin is not rising at a rate greater than one mg. every six hours you can afford to temporize.

Another factor influencing development of kernicterus is perinatal anoxia. The anoxic infant has suffered some injury to the brain and this seems to increase the sensitivity of the brain to bilirubin.

Vitamin K in large doses, that is 10 mgs. or more, in the neonate or very large doses to the mother in labor appears to injure the blood brain barrier to such an extent that kernicterus may appear. It is also thought that Vitamin K in the forms in which we use it may be hepatotoxic and so we may have two factors operating here.

Any cerebral injury will increase the sensitivity of the brain to kernicterus. In familial non-hemolytic jaundice the bilirubin may rise very rapidly to 40 mgms/100 ml. or more. There are nine of these cases on record. Seven died and all had evidence of extensive kernicterus in spite of exchange transfusions. The two who survived were five and seven years old at the time of the report and had no clinical evidence of neurologic disturbance.

Gantrisin given to the neonate increases susceptibility and apparently lowers the blood brain barrier to the extent that kernicterus has been reported in about 90 per cent of prematures receiving it, and many of these were infants whose serum bilirubin never rose above 15 mgms. per cent. Kynex given to the pregnant women is also known to cross the placental barrier and has now been implicated in a few cases of kernicterus.

Other kernicterogenic factors of clinical importance which we may see are: neonatal bacteremia, infectious hepatitis in the mother, and maternal diabetes.

Dr. Ellis:

One very significant result of the basic information given by Dr. Smith is the successful development of the exchange transfusion. I think this has been a very major advance in medicine. With it pediatricians are saving babies that used to die and they are preventing serious complications in the babies who survive. Dr. Brian Moynahan has agreed to discuss this important aspect. Dr. Moynahan.

Exchange Transfusion: Dr. Brian Moynahan.

The exchange transfusion has two fairly simple reasons for being done in newborn babies with hemolytic disease. Number one, you are trying to prevent death in a patient who has potential or actual cardiac failure. Number two, you are trying to prevent hyperbilirubinemia and its possible consequence of kernicterus. You're not getting at the root of the disease. No one yet knows how to do that in cases of hemolytic disease of the newborn.

What the exchange transfusion will do well is to remove many sensitized baby cells and replace them with non-sensitized cells, usually those of an adult. Thus you diminish the reservoir supply of bilirubin for the immediate future. Another important thing accomplished is the regulation of blood volume and this is essential in managing cardiac failure. Many of these newborns, all hydrops certainly, and many of the others are in cardiac failure either severe or mild. By regulation of the blood volume you can help or hinder the degree of cardiac failure. And you may increase the oxygen carrying capacity by increasing the hematocrit of an anemic baby.

You also do other things, though not too well

or too efficiently. You can remove bilirubin from the serum; however, there is not as much of that removed at the time of exchange as you might think. However, with the exchange transfusion you remove some of the bilirubin in the intravascular system and you remove some of the antibody that is harming the baby's cells.

There are certain undesirable effects which you try to minimize when you do the exchange. If you reduce or increase the baby's blood volume too much, you immediately set up the possibility of acute cardiac failure. If you take too long doing the procedure, this danger is increased.

The citrate in ordinary transfused blood is a source of danger. It binds the ionized calcium in the blood in a baby already potentially in trouble because of myocardial anoxia. You may add to its troubles by the removal of the ionized calcium. Because of this, one of the things advocated by some people is the use of heparinized blood in an exchange transfusion.

Electrolyte Imbalance

There may be adverse effects of other electrolyte imbalance. I am sure that no one knows what all these adverse effects are—but there must be many when you use a bottle of citrated blood, sometimes days old, to replace 80 to 90 per cent of the baby's blood. You're accomplishing some rather marked electrolytic changes. However, it does appear that babies are, as the book says, in an excellent state of homeostasis and they usually seem to get over the trouble you are making for them.

Another undesirable effect of an exchange transfusion that must be guarded against is that these babies are known to be thermolabile. They must be guarded against loss of heat. They need oxygen, of course.

While there is quite a bit more known about what to do about these babies than there used to be, in my opinion at least, the final decision as to whether or not to do an exchange transfusion depends on the judgment of the doctor who is looking after the baby. One may use the figure of 20 mgms/100 cc. of bilirubin in the baby's serum as the time you are forced to do an exchange transfusion. Either that, or you have a baby who seems to you will soon have 20 mgms. of serum bilirubin.

Still, as Dr. Smith just said, you may have kernicterus develop at a lower bilirubin level. As far as I'm concerned, you often have warning of a baby that's to be in serious trouble from the antibody titer of the mother's blood. You have to start looking at that baby after it is born and look at it every half hour or so. If jaundice starts in a couple of hours and the Coombs is positive, you might just as well start doing an exchange transfusion immediately.

In some babies with a positive sibling history and a rising antibody titer in the mother in the late months of pregnancy, you'll have an uneventful delivery and an uneventful course in the baby. Here all the tests that can be done cannot replace your own judgment—by looking at the baby and having a nurse that's trained to warn you if the baby becomes jaundiced.

The technique of exchange transfusion varies all over the country but it doesn't vary essentially. The transfusion is generally done by the umbilical vein and its like threading jello when you're trying to get the catheter into the vein. The catheter used is generally a K 30. I use it because it happens to be handy around here, and you have the advantage of not only one opening at the end but side openings too, as in some other catheters. You put the catheter into the umbilical vein, pass it down to a place where you get free passage. Now, in my reading about this, I've learned it might be nice if you measure the venous pressure and that can be done by holding up the catheter vertically and simply measuring the pressure with a ruler.

Venous Pressure

And in the article from which I stole most of my ideas, they say that if the venous pressure is between four and eight cm. of water that's all right, but if it's up around 10 cm. you better start thinking about heart failure. In this case you should take off a fair amount of blood before you start giving it with the hope for a good effect on the state of the heart and the circulation. They advocate taking off between 30 and 60 cc. in such an instance, more if deemed necessary.

Once in your spot—they used to talk about a pool of blood; what actually happens is you find a spot where the vein doesn't collapse around the catheter and the blood seems to come in and out pretty easily. And you stay there and to do so you

tie the catheter down. You may have to move it here and there, but for the most part if you find one good spot you try to stay there, and you have it made.

Exchange Small Amounts

When we first started doing this, we used to exchange 50 cc. or more at a time. And I think we'll all agree—at least I'll agree with myself—it's much easier to exchange smaller amounts. It is easier technically because a large 50 cc. or 30 cc. syringe or even a 20 cc. will stick easily and they are cumbersome to handle. I use a 10 cc. or at most a 20 cc. syringe. I give and take 10 to 20 cc. of blood at a time. I start out getting the blood working with a little saline, and I give the baby about one cc. of aqueous heparin to help keep things from getting clotted up. Then I exchange 10 to 20 cc. at a time, trying to keep things as even as possible.

Calcium Gluconate

About every 100 cc. of exchange, I give the baby one cc. of 10 per cent calcium gluconate. You keep right on doing this until you've finished a unit of blood. At the end, you measure the serum bilirubin, once again use your clinical judgment, and worry about now or later giving a second exchange transfusion. I've had to repeat the exchange two and three times in some babies. This will depend on your clinical judgment of the baby as well as results of laboratory studies.

Fresh blood, of course, is best to use and the fresher the better. When the clinical history or maternal antibody titer suggests trouble, you can have a donor ready and the blood donation obtained shortly before or after delivery. The blood should be of the maternal type and should be crossmatched using donor cells and maternal serum. If there is a choice, the donor should be female. The fact that one should use maternal serum in crossmatching with donor cells makes it possible to have donors available ahead of time, and also one should remember that in the case of ABO sensitization, the maternal blood type will almost always be type O.

Exchange transfusions may be used for problems other than newborn hemolytic disease. Familial hemolytic anemia in crisis, Dr. Smith mentioned. Exchange is also used in poisoning, especially severe salicylism. I understand it is used in adult patients from time to time for intoxications of various kinds.

Of course, we pediatricians are all proud of this because it's about the only time we can make a big fuss, use a lot of blood, get everyone working for us and act like surgeons.

That about sums it up—the exchange transfusion.

Dr. Ellis:

So far, no one has taken their full ten minutes and this is something of a record. The summary of the problem of hemolytic disease of the newborn will be given by Dr. Tandysh. Immediately following this, we will have a discussion period.

Seminar Summary: Dr. Matthew Tandysh.

In summarizing this evening's discussion, we've had examples of hydrops or severe hemolytic disease due to Rh incompatibility, an ABO incompatibility, and a probable accentuated physiological jaundice.

Dr. Smith did an excellent job in reviewing the etiology of kernicterus. I think she mentioned something that is going to be investigated further and will probably add a lot to our knowledge and that's the business of certain drugs aggravating hyperbilirubinemia.

We had the pleasure of having Dr. Louis Diamond in Albuquerque on his way to the West Coast recently. We invited him to a pediatric meeting and he told us that there are quite a number of drugs that are being implicated now. Vitamin K is one, Gantrisin is another, and still others are coming to be recognized. Some of these are being used by obstetricians in sedating their mothers during pregnancy just prior to delivery and these are some of the tranquilizers. Compazine, Thorazine and Phenergan we know can produce jaundice in any patient.

Compete for Glucuronic Acid

It's been shown, according to Dr. Diamond, that these drugs compete for glucuronic acid in the hepatic conjugation process. And so even the child who has no incompatibilities—say, the mother is type A, Rh positive; the baby type A, Rh positive—there is a certain amount of hemolysis that takes place early in the neonatal period and one product of this hemolyzed blood is bilirubin and in a situation where the glucuronic acid is already spoken for, so to speak, then the indirect bilirubin may rise abnormally.

I can't help feeling that much of our excessive

physiological jaundice that we speak about is sort of a coverup for our own ignorance. I'm sure that in days to come we will begin to classify more and more of these so-called physiological jaundices into more specific categories.

One of the drugs mentioned by Dr. Diamond was Dilatin. Mothers who have convulsive disorders may receive Dilatin and this drug has been implicated as a competitor in the glucuronic acid conjugation system.

Also phenacetin, which is a component of our APC pills. Vitamin K and Gantrisin have been mentioned. Chloromycetin, as you know, given to small babies may produce the so-called "grey disease". That is an entirely different syndrome. But Chloromycetin is also detoxidified by the glucuronic acid system and in a newborn baby who has some extra hemolysis it is going to compete with bilirubin.

Heparin Competes

Now, an interesting point brought out at the state meeting by Dr. Day was that heparin may be implicated in competing for the glucuronic system. As both Dr. Smith and Dr. Moynahan mentioned, some people have been very unhappy with citrated blood since this does immobilize the free calcium in the baby's system and have taken to using heparin. Dr. Day feels that heparin will definitely compete for the glucuronic system and may aggravate the situation.

I had two other brief subheadings that I want to mention. Dr. Moynahan covered one very well and that is the problem facing the pediatrician as to when to exchange the baby. There are various charts that have been computed so that if you know the baby is six hours old and its bilirubin is 13 mgms., you can anticipate that he is going to go above 20 mgms. You can exchange him even though his bilirubin is less than 20 mgms. at the time.

With a previous history of exchange transfusion, I think you're justified in transfusing the baby as soon as you know the Coombs is positive.

The problem becomes more difficult when the baby gets unexplained excess jaundice. Here we classify it as a physiological jaundice but then when the baby is 50 some hours old, and we discover his total bilirubin is 19 mgms/100 ml., we are obligated to repeat it. Now at three days of age, the serum bilirubin is 22 mgms/100 ml., we must face the problem of exchanging the baby or sitting and waiting. This is a difficult conflict. The level of 20 mgms/100 ml. is not a precipice. I'm sure that many babies have developed kernicterus with bilirubins below 20 and on the other hand, we have babies where the bilirubin rose to 40 mgms/100 ml. and we've had no measurable cerebral damage.

And of course, one of the problems we are faced with here is the law suit. Given a child who has an I.Q. of 80 who had a bilirubin of 19 when he was a baby; is there any real proof that this low I.Q. is the result of failure to exchange the baby? Also, I don't think that people are fully aware of the risk involved in exchange transfusions. At the best centers, it runs approximately one per cent mortality and this may be higher in other places.

Discussion:

Dr. Tandysh:

I was asked at this time to attempt to answer any questions from the floor or direct them to the right people.

Dr. Ellis:

I'd like to ask Dr. Smith if she remembers the history well enough to know if there might have been a drug involved in case No. 3?

Dr. Smith:

I tried to find this out from the attending physician recently, and I was not able to find a history of drugs.

Dr. Moynahan:

I think there is one other thing I ought to mention. The second case was mine. In 1954, we thought that ABO sensitization did not cause kernicterus. It happened to this child and I had one other since and the same thing happened. ABO problems have to be watched carefully and it might behoove the obstetrician to do ordinary typings on mothers as well as Rh typings. The latter they usually do. Another thing about this case, the lab work concerning the immune anti A antibody titer was not available till several days after delivery.

Dr. Ellis:

At that time we had to send the blood away for an immune type antibody titration

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Dr. Ann Hunt:

I'd like to comment that ABO incompatibility is more common than the Rh incompatibility and both the pediatrician and obstetrician are up a tree because there isn't any prenatal test available other than just the simple typing of the mother's blood to give you any clue that you might have trouble. Therefore, the most important observation is the one that the nurses make in telling you when jaundice first appears and notifying you if the jaundice appears in the first 24 hours. This is about the only clinical clue that you may have a problem due to ABO sensitization.

Dr. Willis Pickel:

Do you think that we are running a risk by giving Thorazine along with Demorol to mothers during labor?

Dr. Tandysh?

I have not had personal experience with this but according to Dr. Diamond there is no question that Thorazine is in competition in the glucuronate system. There must be some explanation for a baby who has no demonstrable incompatibility who runs a bilirubin in the range of 15 to 20 mgms/100 ml. or even higher. What that explanation is I don't know, but I can't help feeling that in some of these cases drugs are definitely implicated. Also, though I don't know what the statistics are, I can't help feeling that the incidence of more than just a mild jaundice is increasing.

Dr. Ellis:

Isn't this particularly true in premature babies?

Dr. Tandysh:

Yes, because they have the additional problem of an immature hepatic system. As a matter of fact, it is interesting how Gantrisin was implicated. A study was made in a New York Hospital in their premature unit, using various combinations of antibiotics, to see if any particular combination was more effective than another in preventing infections in premature babies. In analyzing their results, they were surprised to see that they had lost several babies on a penicillin-Gantrisin combination, due to kernicterus as demonstrated at autopsy. Further investigation revealed that Gantrisin was the offending agent. Consequently, many pediatricians do not use Gantrisin in premature babies either prophylactically or therapeutically.

Dr. Whipple:

Should one not give Gantrisin to the mother?

Dr. Tandysh:

I'm not sure about that. I don't know if Gantrisin passes the placental barrier and if so, to what extent. I don't think Gantrisin has been implicated in causing or aggravating hyperbilirubinemia in term babies. The studies mentioned were in immature babies.

Dr. Ellis:

If there is no further discussion, I would like to thank our speakers for giving us so much interesting and useful information tonight. Our next seminar will deal with the problem of acute renal failure.

Phoenix Surgical Society Plans Series of Meetings

The first meeting of a series for 1960 and 1961 will be held by the Phoenix Surgical Society December 15, 1960, in the Casa Blanca Inn at Scottsdale, Arizona, on the subject of "Extended Operations on the Intestinal Tract." Dr. Owen H. Wangensteen, president of the American College of Surgeons in 1960, will be the speaker.

Three other meetings have been scheduled on February 14, April 11, and May 9, 1961. All except the last will be held in the Casa Blanca Inn in Scottsdale. The place and subject of the final session will be announced at a later date.

The scientific meetings will be held at 8 p.m. and will be preceded by dinner at 6:30 p.m., to which physicians and surgeons of the area are cordially invited. Reservations should be made, not later than a week in advance of each meeting, to Dr. W. H. Cleveland, secretary of the Phoenix Surgical Society, 1313 N. 2nd St., Phoenix, Arizona.

On February 14, 1961, Dr. Richard B. Cattell, chief of surgery at the Lahey Clinic, will speak on "Surgery of the Biliary Tract." On April 11 Dr. William D. Longmire, Jr., professor of surgery at the University of California, Los Angeles, will speak on "Surgery of Thyroids and/or Parathyroids." Speaker for the May 9th meeting will be Dr. Isidor S. Ravdin, president of the American College of Surgeons for 1961. Dr. Ravdin is the John Rhea Barton professor of surgery at the University of Pennsylvania.

Clinical Pathological Conference

R. E. Thomason General Hospital, El Paso

Case No. 1479, September 30, 1960

F. P. Bornstein, M.D., *Editor*

Presentation of case by W. R. Gaddis, M.D.

History: Dr. Nathan Kleban:

A jaundiced 22-year-old unmarried woman was admitted to the hospital on June 18, 1960.

Excessive bleeding after minor injuries harassed the patient beginning at age six when she "nearly bled to death" from trauma suffered in a car accident. Three years before, at age three, splenomegaly was first detected. Neither spontaneous hemorrhage nor excessive menstrual bleeding had occurred.

Evaluation of the splenomegaly was performed in another hospital in January, 1957. A Grade I short blowing systolic heart murmur was heard. Abdomen was slightly obese. Four to five cm. below the left costal margin the tip of the spleen was felt. Liver was not enlarged. Lymphadenopathy was not present.

Blood counts, bleeding and clotting time and platelet morphology were normal. Prothrombin time was variably prolonged. Platelet count was 102,000, Rumpel-Leeds test was positive. Liver function studies were within normal limits except for a slightly elevated alkaline phosphatase. Lupus erythematosus cells were not found.

Chest X-ray, esophagram and upper GI series were normal. Tortuosity of the splenic vein with numerous varices about the stomach but no portal vein obstruction was demonstrated on splenoportagram at the time of splenectomy.

Portal vein pressure was measured but not recorded in the available summary. One pint of blood was given during surgery. Biopsied liver tissue was reported normal. Platelet count rose to 250,000.

Congenital, bilateral, high-frequency perceptive deafness was found by the ENT service, which also discovered speech defect due to hearing loss, enlarged naso-pharyngeal opening and a high palatal arch.

Menstrual cycles with duration of three days and interval of one month lengthened to intervals of two months after splenectomy. There was no menstruation after January, 1960.

An illness which included urinary burning and jaundice lasted for about two weeks in March, 1960. The patient was treated for kidney trouble with pills by a doctor.

Anorexia, nausea and intermittent vomiting began suddenly four days before admission. Nitrofurantin (Furadantin) was prescribed when the patient was seen in the emergency room the next day. Yellow stools without diarrhea, dark yellow urine, jaundice, and swelling of the abdomen and lower legs then appeared, and the patient returned for admission to the hospital. She did not complain of pain.

Family History:

Parents were living and well. There was no known history of any illness in the family similar to that of the patient. Nor was there any known blood or bleeding disorder.

Physical Examination:

T. 99.2; P. 112; R. 22; B. P. 130/80; Wt. 122½ lbs.

The facial skin had a brown mottled appearance. Sclerae were deep yellow. The abdomen was soft. There was an upper abdominal surgical scar. The lower abdomen was protruberant. Deep palpation in the right upper abdominal quadrant provoked slight pain. One examiner described the liver as 3+ enlarged. Pelvic examination was described as probably normal by an Ob-Gyn consultant, who found the uterus and adnexal regions difficult to palpate because of ascites. Ankles and feet were edematous.

Hospital Course:

Following admission the patient complained of abdominal pain only the first night. Temperatures up to 100 were recorded almost daily for two weeks. There was fair appetite and no vomiting. On June 25 one examiner thought a non-tender liver edge was palpable two cm. below the right costal margin. Vague abdominal distress, intermittent jaundice and findings of ascites were described on June 29.

Pathologist's diagnosis of "Tissue invaded by malignant tumor" was made on needle liver biopsy on June 30. The report added: . . . "the material is inadequate for a definite diagnosis."

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Ascitic fluid was removed by paracentesis on several occasions from July 2 to 7. Fluid removed on July 7 was reported: "Positive for tumor cells."

Laparotomy to obtain liver tissue for biopsy was done on July 15. About four liters of bile stained fluid was found in the abdomen. The liver was studded with nodules. "The edge of the liver looked like a bunch of big, black grapes."

Jaundice deepened. The patient became drowsy, restless, confused and died on August 1, 1960.

Laboratory Findings:

X-rays: 6-25-60—Chest: Healthy chest; survey film of abdomen, "findings consistent with ovarian tumor." 7-4-60—Abdomen: Re-examination of the abdomen and comparison with previous study reveals a further haziness and an increase in the size of the previously observed findings consistent with ovarian tumor with accompanying ascites. 7-7-60—Complete skeleton survey and I.V.P. Intravenous pyelogram: "Normally concentrating and draining kidneys. No evidence of obstructive uropathy. No evidence of metastatic bone disease was found in skeletal survey."

Blood counts: 6-20-60: Hb. 12.0 gms., Ht. 48%, WBC 13,400, Eosin. 3, Juveniles 4, Stabs. 7, Segs. 54, Lymphs. 31, Monos. 1; 6-25-60. Hb. 12.0 gms., Ht. 43%, WBC 13,600, Eosin. 3, Segs. 63, Lymphs. 31, Monos. 3; 7-14-60: Hb. 14.2 gms., Ht. 47%, WBC 16,800, Stabs. 6, Segs. 75, Lymphs. 18.

Chemistry: 6-18-60: Van den Bergh Direct—6.75 (Total 13.75), Total Protein—7.2 gm.%, Albumin—3.8, Globulin—3.4, A/R—1.1. 6-22-60: Glucose—77 mg.%, Van den Bergh Direct—4.62, Indirect—8.74; 6-23-60: Glucose—65 mg.%; Phosphatase, Alk.—9.8 units. 6-24-60: Total Protein—7.2 gm.%. 7-1-60: Total Protein—6.8 gm.%, Albumin—3.7, Globulin—3.1, Van den Bergh Direct—5.0. 7-3-60: Total Cholesterol—244, Nonprotein Nitrogen—21, Phosphatase, Alk.—11.8 units, Total Protein—6.6 gm.%, Albumin—3.3, Globulin—3.3, Urea Nitrogen—8.5. 7-6-60; Van den Bergh Direct—5.4, Indirect—10.16. 7-7-60: Urea Nitrogen—8.5. 7-11-60: Van den Bergh Direct—6.48, Indirect—14.52. 7-14-60—Van den Bergh Direct—8.44, Indirect—16.3. 7-15-60: Cholesterol, Esters—92 mg.%.

Sedimentation rate—6-20-60: 26 mm./60 min.

Platelet count—6-20-60: 1,944,720. 6-25-60: 776,600.

Coagulation time—6-20-60: 4′ 20″, bleeding time, 2′ 16″.

Prothombin time—6-20-60: 82%. 6-25-60: 77%.

Thymol turbidity—6-20-60: 2.5 thymol units. 7-1-60: 3.0 units.

Urinalyses—6-16-60: Orange, hazy, acid, S. G. 1.015, Albumin neg., Sugar neg., WBC 2-3, RBCO, Ep. cells few round, casts few finely granular, large amount of mucus. 6-20-60: Bile positive, urobilinogen Pos. 1:80. 6-23-60: Bile positive, urobilinogen negative. 6-30-60: Urobilinogen negative. 7-3-60: Bile strongly positive, urobilinogen pos. 1:100 dil. 7-15-60: Amber, hazy, acid, S. G. 1.010, Albumin neg., Sugar neg., Ep. cells rare sq., 1-2 coarsely granular casts, loaded with motile bacteria.

Coombs tests—6-20-60: Negative. 6-20-60—Negative.

Serology—6-21-60: Negative.

Cephalin flocculation—24 hours negative, 48 hours 1+ (6-22-60).

Erythrocyte fragility—6-23-60: Patient—Initial hemolysis .48%, Complete hemol. .32%. Control—Initial hemolysis: .48%, Complete: .36%. Normal initial—44-40, Normal complete—32-28.

Blood smear—6-24-60: Morphology of red cells reveals them to be microcytic, hypochromic in appearance. There is a left shift in the granulocyte series, otherwise no abnormalities are noted.

Feces—6-22-60: Negative for parasites or ova. 7-6-60: Negative for occult blood, many monilia seen.

Glucose tolerance—6-24-60: Fasting—48 mg.%, Half hour—105 mg.%, 1 hour—150 mg.%, 2 hours—200 mg.%, 3 hours—185 mg.%, 4 hours—140 mg.%.

S.G.O.T.—6-24-60: 76 units.

B.S.P.—6-25-60: 4% retention after 45 minutes. 7-1-60: 40% retention after 45 minutes.

Friedman test—6-28-60: Negative.

Ascitic fluid—7-2-60: S.G. 1.034, Total protein 2.4 gm.%, Albumin 1.5 gm.%, Globulin—0.9 gm.%, bile positive, diff. cell count, 96 lymphs., 4 segs.

Ascitic fluid culture—7-5-60: no growth.

Ascitic fluid for tumor cells—7-2-60: Some mesothelials, and moderate numbers of round inflammatory cells.

Vaginal smear—6-23-60: No tumor cells seen.

Dr. F. P. Bornstein:

I would like to make a few preliminary remarks. There were two liver biopsies taken. The first one was a closed needle biopsy, with the complete result of nothing, which speaks for the value of needle biopsies. The second biopsy showed nothing but tissue invaded by malignant tumor, again a needle biopsy. We had a few clumps of cells which were obviously malignant. I considered the possibility of a neuroblastoma. I rejected it, among other things because of the age of the patient, which is really not a valid consideration on purely morphological grounds.

Clinical Discussion: Dr. W. R. Gaddis:

In spite of the very extensive protocol, you will confess when I am through that I am about as ignorant of the conditions here as could be. But let's state the problem as briefly and as succinctly as possible. Here is a fulminating jaundice and progressive downhill course in a 22-year-old unmarried woman.

We have a positive history of splenomegaly and of a splenectomy, for an apparent thrombocytopenic purpura, 19 years prior to admission to this hospital for this particular illness. To my mind this of course is the chief red herring in the discussion of this case. Has it any pertinent relationship to her final illness?

I would like to review briefly for you the last two paragraphs in the protocol, including the familiar history. There was an illness which included a urinary burning and jaundice lasting for about two weeks in March, 1960. This was some three months prior to her admission to the hospital.

The patient was treated for kidney trouble with pills by a doctor. In the present illness, anorexia, nausea and intermittent vomiting began suddenly four days before admission. Furadantin was prescribed. I don't know the foundation for this, since the drug normally, at least in my patients, causes an increased amount of the same type of symptomatology.

When the patient was seen in the emergency room, the next day, she had yellow stools without diarrhea, dark yellow urine, jaundice, and swelling of the abdomen and lower legs. She did not complain of pain. I would like to point out that the progressive final development of her jaundice was of sudden onset along with the appearance of ascites and edema, dependent type.

Her parents were living and well. There was no known history of any illness in the family similar to that of the patient, nor was there any known blood or bleeding disorder. This patient of course, if you reviewed the history, had had a disorder of the hematopoietic system some time in the years previous.

So examination then on her admission revealed the presence of clinical jaundice, rather marked; ascites, dependent edema, enlargement of the liver, and a questionable "negative" pelvic examination. The examiner stated that he was unable to be certain of his findings on this examination because of ascites.

Whether subsequent examination after paracentesis had been performed might have been of help we don't know. I am going to ask Dr. Ravel if he will discuss the X-rays before I continue with my discussion.

X-Ray Discussion: Dr. Vincent Ravel:

The chest X-rays showed no evidence of metastatic disease to the visualized bony thorax, shoulder girdles of the lung fields. The two survey films of the abdomen revealed the soft tissue haze that is consistent with ascites; there again no evidence of metastatic disease to the lumbar spine or pelvis is seen.

I see no significant intra-abdominal calcification, the psoas shadows are hazy, naturally with the onset of the fluid in the abdominal cavity. We have an intravenous urogram on this patient which was interpreted as being within normal limits, there is no displacement or obstructive uropathy. The bladder contour was regular in outline.

Very frequently in a young person when you have a questionable soft tissue mass in the pelvis with ascites, the ovary is the source of the trouble and so we suggested a possible malignancy or neoplasm of the ovary.

Dr. Gaddis:

To continue then along the lines that we are talking about here in the discussion of this patient: I believe that we saw this patient in our clinical conference on at least two occasions, or discussed the findings relative to her problem. This led to the needle biopsy of the liver which Dr. Bornstein decried and which the surgeons who were present on that occasion also decried, and we finally were able to have an open biopsy done.

Let's look just briefly at this maze of laboratory procedures, and there were a great many of them. I shan't go into them in detail. The patient had 12 grams hemoglobin on admission. For this hospital that's a good report. She did have a persistent leucocytosis. This was present throughout her illness as many times as we sampled her circulating leucocytes.

There was evidence of decreased hepatic function. She had a disturbance of her A/G ratio, she had evidences of edema which may have resulted from that. Her glucose was persistently low which may have represented an inability of the liver to convert the glycogen into glucose. She had an elevation of her serum bilirubin which went up rather high just prior to her death, about 15. If the pediatricians had been taking care of this patient, probably they would have been very concerned about the possibility of central nervous system damage.

Her blood urea nitrogen was not particularly remarkable; as a matter of fact both that and the NPN were low. I felt that the liver function tests as determined were not indicative of inflammatory liver disease. As such we could probably discount the onset of her illness as being due to an inflammatory type disease. Her cephalin flocculation and her thymol turbidity were both within normal limits as reported by the laboratory.

This history is that typical of the onset of acute hepatitis, including the febrile course that the patient had in the hospital. The evidence for the presence of tumor is a positive biopsy and ascitic fluid. We did not find any evidence of blood dyscrasia.

I will discount that one platelet count of over a million. I don't feel that that is germaine. If you are aware of the limitation of the method you must realize that the megakaryocytes will produce platelets and they are not always destroyed as rapidly and consequently one occasionally gets a precipitous rise in platelets which may not necessarily persist throughout the course of the patient's life. Therefore I do not believe this patient had blood dyscrasia.

One presumptive diagnosis that we have to make of this patient is that we have an intermittent obstructive jaundice. She was jaundiced for a relatively brief period of time three months prior to her admission, and only on her final admission did her jaundice become fixed and increase from that time on. If this is due to malignant disease we have to find out whether this is a metastatic lesion or a primary lesion; and what portion of the anatomy it involves.

To produce ascites and jaundice simultaneously a malignancy involves a region very close to the porta hepatis where the three main structures enter the liver; namely, the portal vein, the hepatic artery, and the common duct. Some place along this channel this patient is having an obstructive problem, probably not due to inflammatory disease but rather to the presence of a malignant disease; although this is a young person.

If we can assume from the biopsy that the tumor is at least in one location metastatic, where is it primary? The radiologist has given us some help as to where it probably isn't. It probably is not in a major area which is drained by systemic circulation.

In other words, most commonly tumors outside of the peritoneal cavity metastasize first by way of the blood stream. They are short-circuited into the pulmonary tree. Therefore the tumor must be between the two diaphragms, that is, the respiratory diaphragm and the pelvic diaphragm. It undoubtedly involves chiefly structures which are very close to the portal circulation. One must not discard the idea of widespread peritoneal extension.

Then we must ask ourselves, is the tumor entirely intra-peritoneal, is it retro-peritoneal, or extra-peritoneal; is it portal or extra-portal in its origin? I don't know whether the tumor spread by seeding, or by lymphatic spread, as occurs in the extension of carcinoma from the lower bowel. Could it be primary in the liver? Well, let's survey briefly the things that may give us some indication.

Certain structures within the abdominal cavity are chiefly drained by the portal circulation; namely, the stomach, duodenum, jejunum and ileum. We have to consider structures like a Meckel's diverticulum and the rarer malignancies that happen in appendices, particularly carcinoid tumors. They also happen in the terminal ileum and the colon. The primary lesion could be in the ascending colon, transverse, descending, sigmoid, recto-sigmoid; but not in the anus because the latter drains to structures outside the peritoneal cavity.

It could also be due to a malignancy of the gall bladder itself, of the ampulla of Vater, or of the pancreas. In this patient we can eliminate in all probability the spleen, although accessory spleens do exist. The lymphatic system and any of the reticulo-endothelial structures could be involved,

and this of course includes liver and spleen and other lymphatic structures within the peritoneal and abdominal cavity.

From the genital system we can have extension from the uterus but this is neither common from the fundus nor the cervix. The fundal carcinoma most commonly spreads through the systemic circulation and the cervix through its lymphatics. The ovarian cystoadenocarcinomas have a different spread, namely by peritoneal implantation and local seeding.

I recall operating on a patient in this hospital who had proven gall bladder disease with stones, and in performing the incision to remove the gall bladder we found peritoneal implants in the omentum and the parietal peritoneum from a very small carcinoma of the right ovary. This patient succumbed to this carcinoma within a period of six months, even though the operative procedure otherwise was very satisfactory.

I choose to rule out the presence of carcinoma in the stomach and duodenum, because we have an extreme lack of symptoms or signs which would point to it. We have no blood, for instance, in the stool. This helps us to decide at least that we probably have no open malignancy of the wall. It does not rule out the presence of tumors like lymphosarcomas.

The small bowel tumors of a malignant nature are very uncommon, they usually give rise to some intermittent cramping, distention, and symptoms of intestinal obstruction. This patient had none of these; I don't feel that this fits. The same thing applies to tumors which arise occasionally from the embryologic remnants in a Meckel's diverticulum.

I don't think we can rule out tumors of the large bowel quite as easily. I have seen one carcinoma of the transverse colon in a 16 year old boy; it caused his death. It is quite startling how often a patient can be seriously ill from malignancy extending from an ovary and not have any symptoms. This patient did have a disturbance of her menstrual history. Whether this had any relationship to changes and alterations in her ovarian function would only be conjecture.

I believe she died in hepatic coma and as a result of hepatic failure. But now we must once again pin ourselves down to the most difficult task of deciding where was the origin of this particular tumor. I said very little about the possibility of pancreatic tumor in this patient. We know that she did have a persistent low blood sugar which made me think of some adenocarcinoma of the islets of Langerhan's. They occur very infrequently. They are not common, I assure you. They occur as very small lesions, five mm. in diameter or less, they are very difficult to find. The pancreas could be an ideal site for the origin of this patient's disease, and it would remain relatively quiescent over a long period of time.

So I am going to have to stick my neck out on the basis of what we know from this protocol and from the course and progress of this patient's suffering. I believe that she had a malignant disease which involved the area of the hepatic trinity; of the common duct and portal vein and the hepatic artery with an increasing obstruction to cause her to have an obstructive type jaundice with destruction of the liver and death in hepatic coma. I think the probable primary source of this patient's tumor was the pancreas, although she was a very young woman, and I know that I have probably pinned myself down too well in discussing this; but we have seen a number of patients through the years go through this hospital that have violated the ordinary rules.

Dr. Solomon Heller:

This particular case presents a very fascinating total history and it would be interesting to try to sew the whole thing up into more or less one historical and final end. There was splenomegaly arising or found at the age of three, and later the thrombocytopenia or apparently splenic inhibition or dysplenic disease, which led to the removal of the spleen in 1957. Then came jaundice, obvious ascites, and etc. I would wonder whether this whole thing is not just one picture. The so-called Banti's syndrome has fallen quite a bit in disrepute, but frankly this case seems to fit, until the final phase, into such a syndrome or a congestive splenomegaly.

The etiology has been batted around quite a bit, but it is thought that somewhere along the line there is an obstruction somewhere in the portal system, perhaps the splenic vein, which leads to enlargement of the spleen, later cirrhosis, ascites and so forth. I would wonder whether this patient did not, at the time of the previous surgery, have some underlying cirrhosis; and on top of that developed a hepatic neoplasm.

The primary tumor which may be quite anaplastic may be a primary hepatic sarcoma rather than a metastatic tumor from elsewhere. I feel that this would fit the entire picture very nicely and perhaps too well to be true.

Dr. Pablo Ayub:

I would like to say that the complication of jaundice and ascites would go well with a nodular liver. I think that with the history, the findings, the presence of nodules, the most likely thing is a tumor which obstructs not only the biliary system but the afferent circulation of the liver.

Clinical Diagnosis: Carcinoma of the liver.

Dr. Gaddis's Diagnosis: Primary malignancy of pancreas.

Pathological Diagnoses: 1. Multicentric primary adenocarcinoma of liver arising in cirrhotic liver. **2.** Metastases to lungs. **3.** Extension into gall bladder. **4.** Severe icteric nephrosis.

Pathological Discussion: Dr. F. P. Bornstein:

On autopsy there was an extremely emaciated, fairly young woman. The abdominal cavity contained about 2000 cc. of fluid. The only thing in the chest was a few tiny superficial tumor nodules which were obviously metastatic, and yellow. The liver weighed 2100 grams.

The liver surface was coarsely nodular. The nodules measured between one and two cm. in greatest diameter. Some of these nodules were bluish-green, others grayish-white. The liver cut with increased resistance. On cut section there was total loss of the hepatic pattern. These nodules mainly varied from a few mm. to several cm. Some were confluent, some appeared yellow, and others were hemorrhagic. Thin bands of jaundiced liver tissue were seen between these nodules.

The gall bladder was removed after dissection of the liver. The wall of the gall bladder was found to be intact, and there was no direct invasion from the liver into the wall of the gall bladder. Upon opening the gall bladder we found a pedunculated tumor which arose actually in the cystic duct. The common bile duct was not affected. The mucosa of the gall bladder was pale and flattened out. Stones were absent (Fig. 1 and Fig. 2).

On cut surface you can see the tumor nodules, but you also can see that in addition the bands of fibro-connective tissue are totally irregular, so that you have tumor nodules embedded in a coarsely cirrhotic pattern. Here is a close-up to see the real change in the liver which permits us to say that these are tumor nodules in a cirrhotic liver (Fig. 3).

On further sectioning it becomes obvious, and histology confirmed it, that the polypoid tumor of the gall bladder actually was a tumor nodule that had broken through the wall of the gall bladder. It was not primary of the gall bladder but a direct extension of the liver tumor. This also brings out the point that the shape of tumors is greatly dependent on their seed bed, if they are surrounded by solid tissue they form a different shape from tumors pushing against a soft mucosa.

The diagnosis here is a primary hepatoma in a young woman who already had cirrhosis of the liver, producing obstructive symptoms. On the basis of this cirrhosis she developed a hepatoma. If we would see this pattern in a person 30 years older we wouldn't be too surprised. I think Dr. Heller's speculation that the splenectomy was done in an earlier stage of the process, already non-malignant hepatic damage, is quite correct.

Dr. Gaddis:

I would like to say one thing in closing. Of course this has not made me feel very different. I think I pretty well got to say at least all the things that produced the external symptoms as far as this patient is concerned. I am distrubed by the presence of a primary hepatoma in this age group. This is not to say it couldn't happen; it shouldn't happen. The one case that I have seen previously was in a liver which grossly appeared normal though much enlarged. This present patient had cirrhosis to start with and the nodularity of her tumor was due to the cirrhosis.

Fig. I

Fig. II

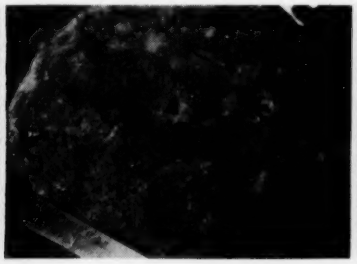
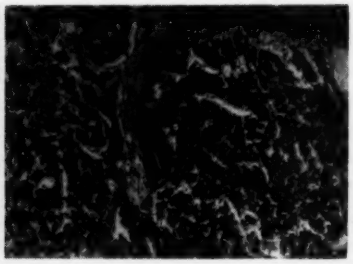
Fig. III